

**REMARKS**

Claims 1, 3, 5-7, and 9-13 are pending in the present application. Claims 2, 4 and 8 have been cancelled. No new matter has been added by way of the present amendment. For instance, three trademark identifiers have been added to the specification. The first line of the specification has also been amended to reference priority information. The Abstract has been amended to remove the word "said." In the claims, the recitation of "derivative thereof" has been removed with respect to the SEB having the substitution. The wording of the claims has also been amended to avoid the use of the word "modifications." Also, the phrase "on the basis" has been clarified in the claims. Claim 1 has also been amended to include textual subject matter taken from originally filed claims 2, 4 and 8. Lastly, non-elected subject matter has been removed from claim 13. Accordingly, no new matter has been added.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

***Objection to the Abstract***

The Examiner has objected to the Abstract of the Disclosure asserting that the recitation of "said" is legal phraseology and should be avoided. Applicants traverse and submit that the Abstract of the Disclosure has been amended to remove the

recitation of "said". Accordingly, this objection is moot. Reconsideration and withdrawal thereof are respectfully requested.

***Objections to the Specification***

The Examiner has objected to the specification for the reasons recited at page 3 of the outstanding Office Action.

First, the Examiner asserts that the first paragraph of the specification does not accurately reflect the status of the prior application, in particular, the "priority" application. Applicants traverse and submit that the first paragraph of the specification has been amended to correct this issue.

Second, the Examiner asserts that the use of trademarks in the present specification should be respected. Applicants have corrected trademarks located in the present specification, for instance, the recitations of "Salazopyrin" on page 2, line 8, "CIRCLEGROW" on page 25, line 17, and "Sepharose" on page 26, line 2. Additionally, the Examiner has pointed to "Invitrogen" at page 21, line 14 as an additional possible trademark. Applicants submit that this is the name of a company, not a trademark. Likewise, the following list refer to other names of companies, not trademarks, referred to in the present specification.

- (i) "CLONOTECH" on page 21, line 6;
- (ii) "Pharmacia Biotech" on page 22, line 12;

- (iii) "Perkin Elmer Cetus" on page 22, line 18;
- (iv) "BIO 101" on page 25, line 17;
- (v) "Pharmacia" on page 29, line 6;
- (vi) "Falcon" on page 29, line 9 and on page 30, line 3;  
and
- (vii) "Biosource" on page 29, line 13.

In summary, Applicants submit that each of the Examiner's objections to the specification have been addressed. Reconsideration and withdrawal thereof are respectfully requested.

***Issues Under 35 U.S.C. § 112, First Paragraph***

The Examiner has rejected claims 1-5 and 8-13 under 35 U.S.C. § 112, first paragraph, for the reasons recited at pages 3-5 of the outstanding Office Action. Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that there is insufficient written description for the recitation of "derivatives thereof" in the present claims as encompassing derivatives of SEB or derivatives of modified SEB. Applicants respectfully submit that the recitation of "derivatives thereof" with respect to SEB have been removed from the present claims. Accordingly, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

***Issues Under 35 U.S.C. § 112, Second Paragraph***

The Examiner has rejected claims 1-5 and 8-13 under 35 U.S.C. § 112, second paragraph, for the reasons recited at pages 5-6 of the outstanding Office Action. Applicants respectfully traverse each of these rejections. For clarity sake, each of the following sub-headings match the sub-headings used by the Examiner under Item 13 of the outstanding Office Action.

(a) The Examiner has rejected claim 1 asserting that the recitation of "comprising as an active ingredient, modifications of... SEB..." is indefinite. In particular, the Examiner asserts that "modifications" refers to a process, not a product. Applicants traverse and submit that claim 1 has been amended to clarify the nature of the SEB active ingredient. Also, the recitation of "modifications" no longer appears in the claim.

(b) The Examiner has rejected claim 1 asserting that the recitation of "modifications" with respect to SEB is indefinite since it is unclear whether the claimed product is a mixture of multiple molecules of modified SEBs, or one molecule of SEB with multiple modifications within the molecule. Applicants traverse and submit that claim 1 has been amended to avoid this issue. In particular, the claim has been clarified such that SEB has a substitution of at least one amino acid residue.

(c) The Examiner has rejected claims 2 and 3 for the recitation of "said SEB modifications or derivatives thereof are SEB having amino acid substitution at the 9-position", asserting

that it is unclear how a substitution at one position can be called "a modifications". Applicants traverse and submit that this language has been removed from the claims.

(d) The Examiner has rejected claims 4 and 5 for similar reasons as discussed in item (c) above. The claims have been amended to remove this issue.

(e) Similar to items (c) and (d) above, the Examiner has likewise rejected claims 8 and 9. Applicants traverse and submit that the claims have been amended to remove this issue.

(f) The Examiner has rejected claims 1-5, 8 and 9 for the recitation of "derivatives", asserting it is unclear what is encompassed by this recitation. Applicants traverse and submit that the recitation of "derivative" with respect to the SEB has been removed from the claims.

(g) The Examiner asserts that claim 1 is vague and indefinite for the recitation of "natural type SEB" and "wild-type SEB", asserting it is unclear how the two SEBs differ from one another structurally or functionally.

Applicants respectfully submit that there is no substantial difference either structurally or functionally between the "natural type SEB" and the "wild-type SEB", the former referring to an enterotoxin purified from a bacterial culture and the latter referring to the "natural type SEB" to be prepared by genetic engineering techniques as explained on page 27, lines 20 to 24 of the specification.

(h) The Examiner has rejected claim 1 for the use of the non-legal language "they". Applicants traverse and submit that this language has been removed from the claims.

(i) The Examiner has rejected claims 2-5, 8 and 9 asserting that the recitation of "substitution... on the basis of natural type SEB" is unclear as to what is meant by "substitution on the basis of natural type SEB". Applicants traverse and submit that this phrase is intended to mean that the modified SEB is an amino acid substitution occurring at a specific amino acid residue in natural type SEB. For instance, "amino acid substitution at the 9-position on the basis of natural type SEB", as in original claims 2 and 3, means that the modified SEB has an amino acid sequence which if compared to natural type SEB, would reveal that the amino acid at the 9-position is substituted. To clarify this issue, Applicants have amended the relevant claims to recite that the SEB has an amino acid substitution at a position corresponding to the 9-position (or 23-position or 44-position) of the natural type SEB.

(j) The Examiner has rejected claim 13 asserting that it includes non-elected subject matter. Applicants traverse and submit that claim 13 has been amended such that it no longer depends upon non-elected claims 6 and 7.

(k) The Examiner has rejected claims 2-5 and 8-13 asserting that they are vague and indefinite for being dependent either directly or indirectly upon claim 1, which has been rejected for

the reasons discussed above. Applicants traverse and submit that the rejections to claim 1 have been rendered moot by the present amendment.

In summary, Applicants respectfully submit that the presently pending claims encompass subject matter which fully satisfies the requirements of 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of all outstanding rejections are respectfully requested.

***Issues Under 35 U.S.C. § 102(b)***

The Examiner has rejected claims 1 and 13 under 35 U.S.C. § 102(b) as being anticipated by Canadian Patent 2,084,120 A1 or WO 96/40235. Applicants respectfully traverse this rejection.

Claim 1 has been amended to include the subject matter of claims 2, 4 and 8, in the alternative. Claims 2, 4 and 8 were not rejected by the Examiner as being anticipated by the above references. Accordingly, the inclusion of this textual subject matter into claim 1 renders this rejection moot. Reconsideration and withdrawal there are respectfully requested.

The Examiner has also rejected claims 1-5 and 8-13 under 35 U.S.C. § 102(e) as being anticipated by WO 93/14634. Applicants respectfully traverse this rejection.

**The Present Invention**

The characteristic features of the present invention are

based on the finding that SEB, having been thought to be a causative agent of food poisoning etc. as an exotoxin, is efficacious for prophylaxis/remedy of immunopathy such as autoimmune disease. The present inventors have prepared modifications of SEB with reduced toxicity for use in the prophylaxis/remedy and for the first time proved the therapeutic effects of the modifications on the prophylaxis/remedy through oral administration thereof in mouse CIA model (mice collagen-induced arthritis) established as a model for human rheumatoid arthritis (cf. Examples 6 and 7 of the present specification).

Distinctions Between the Present Invention and WO 93/14634

The technique disclosed in WO 93/14634 (WO '634) has been acknowledged by the present inventors at the time when the instant application was filed as referred to on page 5, line 6, of the specification (referenced as Japanese Patent Publication No. 8-500328). WO '634 relates to (1) preparing modifications (mutations)/derivatives with reduced toxicity of SEB, as a representative of a superantigen, from the viewpoint of its structure; and (2) prophylaxis and remedy for diseases induced by toxicity of superantigen by an antibody elicited by administration of said modifications (mutations)/derivatives of SEB as an antigen (claims, page 18, the last phrase, and Example 7 on page 35).

However, WO '634 differs from the present invention in the



diseases to which modifications (mutations)/derivatives are to be administered, and in the action and mechanism thereof, in short, in their technical idea *per se*. For example, the technical idea of WO '634 is reflected in the wording in claims: "A method for preventing the toxic effects of a superantigen by treatment with a molecule, wherein said molecule elicits antibody production without inducing T cell activation", which is different from the technical idea of the present invention.

WO '634 merely discloses preparing modifications (mutations)/derivatives of SEB, i.e. a technique for reducing toxicity of SEB when administered into the living body. However, WO '634 fails to disclose or suggest that such modifications (mutations/)/derivatives of SEB with reduced toxicity could be used for prophylaxis/remedy of autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, etc. with high safety.

The description of WO '634 on pages 12-14 and 17 merely collectively discloses the knowledge at the time when that application was filed. For example, WO '634 discloses that the modifications (mutations)/derivatives of SEB interact with the V $\beta$  elements of T cell receptors in a way which leads to modifications in the way T cells respond to a superantigen, including deletion or inactivation/desensitization of T cells as well as enhancing T cells. Specifically, WO '634 discloses that "The molecules of this invention can function in this manner, i.e., by leading to deletion or inactivation/desensitization of

at least one or more subpopulations of T cells which present a particular V $\beta$  element" (page 14, lines 20-24), which is indeed different from the present invention, i.e., "without inducing elimination of T cells having specific V $\beta$  component, the elimination being normally induced by natural type SEB or recombinant wild-type SEB" (claim 1 of the present invention).

Moreover, the present inventors have proven in Examples 6 and 7 that the SEB modifications or derivatives thereof of the present invention are efficacious via oral administration. It should be noted that orally administered SEB modifications/derivatives have never hitherto been disclosed nor suggested in the prior art for the fear that SEB might be a cause of diseases such as food poisoning.

In summary, Applicants respectfully submit that the prophylaxis/remedy for autoimmune diseases for the present invention is fully distinguished from the cited art of WO 93/14634. In particular, no anticipation exists. Reconsideration and withdrawal of the outstanding rejection is therefore requested.

In view of the above, Applicants respectfully submit that the present claims define subject matter which is patentable. The Examiner is therefore requested to withdraw all outstanding rejections and allow the currently pending claims.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of three (3)

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months to April 6, 2004 in which to file a reply to the Office Action. The required fee of \$950.00 is enclosed herewith.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie (Reg. No. 42,874) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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By 

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